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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/009,846	01/20/1998	ROBERT ZAMBIAS	5925-061-999	7948

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EXAMINER
PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 05/06/2003

43

Please find below and/or attached an Office communication concerning this application or proceeding.

43

Office Action Summary

Application No.	Applicant(s)
09/009,846	Zambias et al
Examiner	**Art Unit**
Padmashri Ponnaluri	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *2/13/03 and 2/27/03*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *10-13, 17, 18, 22-24, and 26* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-13, 17, 18, 22-24, and 26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 40
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CAR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CAR 1.114, and the fee set forth in 37 CAR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CAR 1.114. Applicant's submission filed on 2/13/03 has been entered.

2. The preliminary amendment K, filed on 2/13/03 has been fully considered and entered into the application.

3. Claims 10-13, 17-18, 22-24 and 26 are currently pending and are being examined in this application.

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 10-13, 17-18 and 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung et al (Advance ACS Abstract, vol. 8, No. 1, January 1, 1995) and Gallop et al (Journal of Medicinal Chemistry, vol. 37, No. 9, April 29, 1994, pages 1233-1251).

The instant claims briefly recite a method of making a spatially-addressable combinatorial array of at least 500 different compounds by providing at least 500 different reaction vessels organized into array and each vessel contains substantially one compound.

Pirrung et al teach non-peptide Indexed library and a method for preparation and screening against acetylcholine esterase of the non-peptide "indexed" combinatorial library. The reference teaches a combinatorial library composed from nine alcohols and six isocyanates (refers to reactants of the instant claims) to formally generate 54 carbomates. The reference teaches to deduce most active member of the library, it was prepared as 15 sublibraries (refers to sub arrays of the instant claims) in which one of the reacting component was fixed (refers to molecular core of the instant claims) and the other reactant used in equimolar mixtures. The reference teaches that the product mixtures were tested and their activities used as indices to the rows and columns of a two dimensional matrix (refers to spatially addressable array of the instant claims) reflecting the actives of individual carbomates. The reference teaches that the indexed libraries offer the

advantage that they can be prepared from any class of compounds composed of multiple subunits and that any class type of assay can be used because **all compounds are generated in free form** (refers to in solution of the instant claims).

Pirrung et al teach indexed libraries. The reference teaches that the product mixtures were tested and their activities used as 'indices' to the rows or columns of a two dimensional matrix reflecting the activities of individual carbomates. A number of carbomates in the most active row and column were synthesized and assayed demonstrating that the most active cell (refers to the reaction vessel of the instant claims) in the matrix could be identified using sublibrary synthesis procedure.

The claimed invention differs from the prior art teachings by reciting combinatorial array of at least 500 different compounds and the reaction vessels contain substantially one compound per vessel. Pirrung et al teach indexed combinatorial library , and the advantages of the indexed library. Pirrung et al teach indexed libraries can be prepared from any class of compounds composed of multiple subunits and that any type of assay can be used because all compounds are generated in free form. Pirrung et al do not teach 500 different compounds in 500 reaction vessels and substantially a single compound in each vessel.

Gallop et al review combinatorial techniques and the screening methods. Gallop et al teach that depending on the number of individual compound sin a library (N) depends on the number of building blocks (b) (reactants) available for each step, and the number of reaction steps in reaction scheme (x), and $N= b^x$. i.e., the reference teaches that using 100 building blocks permits

the theoretical synthesis of 100 million tetrameric chemical entities (page 1234, and figure 1). Thus, it would have been obvious to one skilled in the art to prepare a combinatorial library of 500 different compounds using the formula given by Gallop et al. Gallop et al teach a method for preparation of a combinatorial library by the split synthesis method (i.e., see page 1242, and figure 2). Gallop et al further teach combinatorial libraries of soluble peptides (i.e., see page 1245, right column). The reference teaches that the "split synthesis" algorithm is easily adapted to generating equimolar mixtures of **soluble peptides** that may be screened in a variety of competition binding or functional bioassays. Gallop et al review the work of Houghten et al, bioactive peptides having been identified from libraries containing more than 50 million different sequences.

Thus, it would have been obvious to a person skilled in the art at the time the invention was made to use the split method synthesis of soluble peptides taught by Gallop et al with indexed library synthesis method taught by Pirrung et al and use 500 different vessels to obtain 500 different compounds in the library, because Pirrung et al teach indexed libraries by preparing 15 different libraries, and Gallop et al teach a method for split synthesis and solution synthesis and a method to determine the number of individual units in a library. A person skilled in the art would have been motivated to use the indexed library of Pirrung et al to synthesize a combinatorial library of 500 different compounds in 500 reaction vessels or wells because Pirrung et al teach that the method can be prepared using any class of compounds and can be used for any type of assay because all compounds are generated in a free form and Gallop et al teach the advantages of use combinatorial library of compounds in drug discovery. Further Gallop et al teachings

motivate to determine the number of individual compounds in a library depending on the number of reactants used each step, and the number of reaction steps in a reaction scheme.

7. Claims 10-13, 17-18 and 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung et al (Advance ACS Abstract, vol. 8, No. 1, January 1, 1995) and Rebek, Jr. et al (US Patent 5,877,030).

The instant claims briefly recite a method of making a spatially-addressable combinatorial array of at least 500 different compounds by providing at least 500 different reaction vessels organized into array and each vessel contains substantially one compound.

Pirrung et al teach non-peptide Indexed library and a method for preparation and screening against acetylcholine esterase of the non-peptide "indexed" combinatorial library. The reference teaches a combinatorial library composed from nine alcohols and six isocyanates (refers to reactants of the instant claims) to formally generate 54 carbomates. The reference teaches to deduce most active member of the library, it was prepared as 15 sublibraries (refers to sub arrays of the instant claims) in which one of the reacting component was fixed (refers to molecular core of the instant claims) and the other reactant used in equimolar mixtures. The reference teaches that the product mixtures were tested and their activities used as indices to the rows and columns of a two dimensional matrix (refers to spatially addressable array of the instant claims) reflecting the actives of individual carbomates. The reference teaches that the indexed libraries offer the advantage that they can be prepared from any class of compounds composed of multiple subunits

and that any class type of assay can be used because **all compounds are generated in free form** (refers to in solution of the instant claims).

Pirrung et al teach indexed libraries. The reference teaches that the product mixtures were tested and their activities used as 'indices' to the rows or columns of a two dimensional matrix reflecting the activities of individual carbomates. A number of carbomates in the most active row and column were synthesized and assayed demonstrating that the most active cell (refers to the reaction vessel of the instant claims) in the matrix could be identified using sublibrary synthesis procedure.

The claimed invention differs from the prior art teachings by reciting combinatorial array of at least 500 different compounds and the reaction vessels contain substantially one compound per vessel. Pirrung et al teach indexed combinatorial library , and the advantages of the indexed library. Pirrung et al teach indexed libraries can be prepared from any class of compounds composed of multiple subunits and that any type of assay can be used because all compounds are generated in free form. Pirrung et al do not teach 500 different compounds in 500 reaction vessels and substantially a single compound in each vessel.

Rebek, Jr. et al teach methods for forming combinatorial libraries. Rebek et al teach that a plurality of core molecules (refers to the core molecule of the instant claims) are reacted with a plurality of different tool molecules (refers to the structural diversity elements of the instant claims) to form a library of molecules having non-naturally occurring molecular diversity (i.e., see the abstract). Rebek Jr et al teach that by combining naturally and non-naturally occurring core

molecules an d tool molecules in accordance with the method disclosed, the invention provides a simple process for creating a combinatorial library of vast molecular diversity. The reference teaches that the disclosed solution phase synthesis of combinatorial library generates tens of molecular diversity molecules (i.e., see column 4) (refers to at least 500 compounds of the instant claims). The reference discloses the examples of core molecules (i.e., see column 9 and figure 1), and the tool molecules (i.e., see column 9, figs. 2, 3) useful in the disclosed invention. The reference teaches synthesis of combinatorial library containing 1225 different molecules (example 2) or 10,440 different molecules (example 3) or 97,461 different compounds (example 4).

Thus, it would have been obvious to a person skilled in the art at the time the invention was made to use the different core molecules and tool molecules taught by Rebek. Jr et al with the indexed library synthesis method taught by Pirrung et al to obtain at least 500 different compounds. A person skilled in the art would have been motivated to use the indexed library of Pirrung et al to synthesize a combinatorial library of at least 500 different compounds in 500 reaction vessels or wells because Pirrung et al teach that the method can be prepared using any class of compounds and can be used for any type of assay because all compounds are generated in a free form with a single compound in each cell and Rebek Jr et al teach the advantages of the use of different core structures with tool molecules to obtain more than thousand molecular diversity compound library.

8. *Applicant's arguments filed on 2/13/03, regarding the art rejection of record (office action mailed on 8/16/02) have been fully considered but they are not persuasive.*

Applicants argue that Pirrung et al and Gallop do not teach 'each reaction vessel contains substantially only one compound after chemical reactions are completed. Applicants arguments have been considered but are not persuasive. Pirrung et al teaches that the product mixtures were tested and their activities used as 'indices' to the rows or columns of a two dimensional matrix reflecting the activities of individual carbomates. a number of carbomates in the most active row and column were synthesized and assayed demonstrating that the most active cell (refers to the reaction vessel of the instant claims) in the matrix could be identified using sublibrary synthesis procedure. Thus, each row or column has one individual compound. Thus, if *n* reaction vessels have been arranged as rows and columns and n compounds are prepared, each reaction vessel would have only one *compound which would refer to one compound per vessel.*

Gallop et al teach solid phase split pool synthesis method in synthesis of combinatorial library and use of the method in preparation of soluble peptides. And Pirrung et al teach the advantages of the solution phase synthesis of compounds in an array. Thus it would have been obvious to one skilled in the art to combine the teachings of split pool synthesis method taught by Gallop et al with the indexed library synthesis taught by Pirrung et al.

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Primary Examiner
Technology Center 1600
Art Unit 1639
01 May 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER